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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/819,401	03/27/2001	Laurent Humeau	397272000700	3802

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EXAMINER
LI, BAO Q

ART UNIT	PAPER NUMBER
1648	14

DATE MAILED: 10/10/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/819,401	HUMEAU ET AL.	
	Examiner	Art Unit	
	Bao Qun Li	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *July 24, 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-6 and 8-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-6 and 8-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1, 3-6 and 8-21 are pending.

Response to Amendment

This is a response to the amendment, paper No. 13, filed 07/24/02. Claims 2 and 7 have been canceled. Claims 8-21 have been added. Claims 1, 3-6 and 8-21 are considered before the examiner.

Please note any ground of rejection(s) that has not been repeated is removed. Text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

New matter

The amendment filed paper no. 13, 07/24/2002 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: (1). In claim 1, line 2: " by direct interference of said virus' integration and in lines 5-6: "from copies of said virus that would have integrated into the cell's genome", and (2). Claim 18, the method of claim 1 wherein said conditionally replicating vector further comprises an anti-viral payload.

Applicant is required to cancel the new matter in the reply to this Office Action.

New matter Rejection

Claim 1 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In the instant case, the amendment of claim 1, line 2, "by direct interference of said virus' integration, in lines 5-6: "from copies of said virus that would have integrated into the cell's genome", and in newly added claim 18: "the method of claim 1 wherein said conditionally replicating vector further comprises an anti-viral payload" are not disclosed in specification as it was original filed.

Applicants are required to cancel the new matter to overcome the rejection.

Sequence requirements

This application contains sequence disclosures on page 69 to 71, in which the sequence identification numbers are missing.

Full compliance with the sequence rules is required in response to this Office Action as stated in the previous office action. Applicants are reminded that Applicants have not respond to the office regarding the sequence requirement on paper no. 13, and the failure to fully comply with **both** these requirements in the time period set forth in this office action will be held non-responsive.

Information Disclosure Statement

The information disclosure statement filed on paper No. 6, 01/15/2002, fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. The references that we cannot found in the files or we cannot found in the database have been placed in the application file, but the information referred to therein has not been considered.

In response to the office requirement, the applicants only provided some copies of the documents listed on PTO-1449, which is filed in on paper No. 11, April 23, 2002, the undersigned stated that the remaining documents would be provided at a later date.

However, the office has not received any more documents from Applicants since then. Therefore, the non-submitted documents will not be considered as listed in the copy of the PTO 1449 form.

Claim Rejections - 35 USC § 112

Claims 1, 3-6 and 8-21 are still rejected under 35 U.S.C. 112, second paragraph on the same ground as stated in the previous office action, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is still vague and indefinite in that the metes and bonds of cited "viral DNA", "a virus" and "a viral vector" are not defined.

Applicants argue that when read in the light of the specification, without reading limitation into the claims, the terms are clear to the skilled artisan as directed to the claimed methods of inhibiting the replication of the DNA of a virus by use of a conditionally replicating viral vector that interferences with the integration of the virus into the host cell genome. Applicants further note that the claims need not be imitated to the use of a particular virus or particular viral vector. Instead, all that is necessary is for the conditional replicating viral vector to interfere with integration of the virus into a cell's genome.

Applicants' argument has been respectfully considered; however, it is not found persuasive because there are may viral vector is a conditional replicating vector, such as adenovirus vector, HSV vector and adeno-associated virus vector. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Furthermore, it is still unclear whether the virus and viral DNA as well as the viral vector are intended to be the same virus or a different one. If Applicants wish to claim a particular virus and a particular viral vector, the claim should point out which vial vector and virus is intended. This affects the dependent claims 3-6 and 8-21.

Claims 1 and 3-6 are still rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01.

Applicants submitted that the issue of this rejection is not fully understood. Moreover, applicants amended the claim in order to overcome the rejection.

Applicants' argument as well as the amendment on paper No. 13, has been respectfully considered; however, it is not found persuasive because the process of using the claimed method is not clearly. The omitted steps are how to check the viral vector being function at the direct inhibition of wild-type virus integration step and how to determine the viral vector preventing the production of the viral DNA from the copies of said virus that would have integrated into the cell's genome. When and how the host cells should be treated with viral vector. The omitted structural cooperative relationship between the virus and viral vector is also not clearly in the claims. For example, what is the structural and functional differences between the viral vector and virus, how the viral vector is specifically designed to inhibit a virus DNA integration. What

kind of the molecule that viral vector is carried that enable the vector to exhibit such specific inhibitory function etc. Therefore, the rejection is maintained.

Claim Rejections - 35 USC § 112

Claims 1, 3-6 and 8-21 are rejected under 35 U.S.C. 112, first paragraph on the same ground as stated in the previous office action, because the specification, while being enabling for a method of constructing a conditionally replicating HIV vector (crHIV) comprising a ribozyme expressing cassette for expressing ribozyme molecule(s) encoded by SEQ ID NO: 3 or 4 in either single, double or triple tandem repeats, which is able to cleavage the wild-type HIV virus or helper virus or helper vectors specifically in an in vitro cell line sitting system, does not reasonably provide enablement for having a method for preventing or inhibiting any or all viral DNA replication by using any or all viral vector with comprising any or all kind of nucleotide sequences in vitro as well as in vivo. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicants argue that the rejection made by examiner has provided no objective reason why one skilled in the art would not able to practice this invention in a manner commensurate with the scope of the claims. Accordingly, the emphasis on gene expression and alleged unpredictability thereof are not relevant to the instant claims.

Applicants also argue that the claims need not to be limited to the use of a particular virus or a particular viral vector. Instead, all that is necessary is for the conditionally replicating viral vectors.

Applicants' argument of paper No. 13 of amendment B, filed on July 24, 2002 has been fully considered; however, it is not found persuasive because the claimed method is directed to use a gene therapy approach for treating HIV infection. This approach is totally dependent on the expression of ribozyme molecule by the vector. According to the state of the art, a sustained expression of ribozyme b a vector does humble the progress of this gene therapy of HIV infection as stated in the previous office action.

Moreover, the specification does not teach how to make other conditional replication viral vectors rather than crHIV and lacks the evidence other conditional replication viral vector

would be suitable for the same application of inhibition of HIV infection or other virus infection.

Still further, Applicants does not address other issues related to the safety concern of using the viral vector for treatment of a viral infection, which has a potential to generating a replication competent virus as described in the previous office action.

In addition, the scope of the newly amended claim 1 is directed to the ribozyme directly interference on the integration of HIV into the host genome. However, the specification does not teach how the ribozyme is particularly designed for targeting at this step and it is deficient for support that the disclosed the crHIV with an activity against HIV infection is through this particular mechanism of interfering the HIV integration.

Because the breadth and scope of claims read on Gene Therapy, Applicants are reminded that the field of Gene Therapy is a highly unpredictable field and the applicants have not shown that the any or all viral vector of the invention are able to render a positive results in an in vivo setting system or human being. These fields are highly unpredictable, whether in gene therapy or vaccine development. Especially considering the general and broad statements in the claims. To support the above statements the applicant is respectfully directed to the NIH report (Orkin et al, 1995), wherein the panel of experts concluded that although the promise of gene therapy appears great, the clinical efficacy has not been demonstrated, and significant problems remain in all basic aspect of gene therapy. In addition, the article by Verma et al (Nature, 1997) see page 241, last paragraph, is worth noting regarding the unpredictability in the field and lack of sustained expression of the therapeutic genes. There are no teaching regarding this subject matter with respect to selective effect, sustained delivery and expression of therapeutic genes.

Therefore, considering the broad scope of the claims, unpredictable field and the limited in vitro disclosure, it is still concluded that a skilled artisan would have to conduct undue and excessive experimentation in order to practice the claimed invention. The rejection is maintained.

Double Patenting

Claims 1, 3-6 and 8-21 are still rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14 of U.S. Patent No.

5,888,767A. Although the conflicting claims are not identical, they are not patentably distinct from each other because the conflict claims have overlapping scope of the claimed invention.

Applicants argue that the cited reference does not teach or suggest or indicate the invention is directed to the inhibition of viral integration.

Applicants argument has respectfully considered; however, it is not persuasive because the present application claims to use the same structurally and functionally conditional replication HIV vector (crHIV) to inhibit the HIV infection. The rejection is, therefore, maintained unless applicants officially file a terminal disclaimer (TD).

Claims 1, 3-6 and 8-21 are still rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-15 of U.S. Patent No. 5,886,806A on the same ground as stated in the previous office action. Although the conflicting claims are not identical, they are not patentably distinct from each other because the conflict claims have overlapping scope of the claimed invention.

Applicants argue that he cited reference does not teach or suggest or indicate the invention is directed to the inhibition of viral integration.

Applicants' argument has respectfully considered; however, it is not persuasive because the present application claims to use the same structurally and functionally conditional replication HIV vector (crHIV) to inhibit the HIV infection. The rejection is, therefore, maintained unless applicants officially file a terminal disclaimer (TD).

Claims 1, 3-6 and 8-21 are still rejected under the judicially created doctrine of obviousness-type double patenting on the same ground as stated in the previous office action, as being unpatentable over claims 1-34 of U.S. Patent No. 6,114,141A. Although the conflicting claims are not identical, they are not patentably distinct from each other because the conflict claims have overlapping scope of the claimed invention.

Applicants argue that he cited reference does not teach or suggest or indicate the invention is directed to the inhibition of viral integration.

Applicants argument has respectfully considered; however, it is not persuasive because the present application claims to use the same structurally and functionally conditional

replication HIV vector (crHIV) to inhibit the HIV infection. The rejection is, therefore, maintained unless applicants officially file a terminal disclaimer (TD).

Claims 1, 3-6 and 8-21 are still rejected under the judicially created doctrine of obviousness-type double patenting on the same ground as stated in the previous office action, as being unpatentable over claims 1-28 of U.S. Patent No.6,168,953B1. Although the conflicting claims are not identical, they are not patentably distinct from each other because the conflict claims have overlapping scope of the claimed invention.

Applicants argue that he cited reference does not teach or suggest or indicate the invention is directed to the inhibition of viral integration.

Applicants argument has respectfully considered; however, it is not persuasive because the present application claims to use the same structurally and functionally conditional replication HIV vector (crHIV) to inhibit the HIV infection. The rejection is, therefore, maintained unless applicants officially file a terminal disclaimer (TD).

Claims 1, 3-6 and 8-21 are still rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-32 of U.S. Patent No.6,232,120B1. Although the conflicting claims are not identical, they are not patentably distinct from each other because the conflict claims have overlapping scope of the claimed invention.

Applicants argue that he cited reference does not teach or suggest or indicate the invention is directed to the inhibition of viral integration.

Applicants argument has respectfully considered; however, it is not persuasive because the present application claims to use the same structurally and functionally conditional replication HIV vector (crHIV) to inhibit the HIV infection. The rejection is, therefore, maintained unless applicants officially file a terminal disclaimer (TD).

Claim Rejections - 35 USC § 102

Claims 1, 3-6, 8, 9, 14-16, 19-21 are still rejected under 35 U.S.C. 102(a) as being anticipated by Mautino et al. (Human Gene Therapy Sep. 2000, Vol. 11, pp. 2025-2037) on the same ground as stated in the previous office action.

Applicants argue that Mautino et al. provide no teaching, suggestion or indication of a method to inhibiting virus infection by interference with viral integration with a conditionally replicating viral vector.

Applicants' argument has been respectfully considered; however, it is not found persuasive because this limitation was not present anywhere in the application as it was original filed. This limitation is therefore, a new matter and should not be entered as well as read into the claims. Hence, the rejection is maintained.

Claims 1, 3-6, 8, 9, 14-21 are still rejected under 35 U.S.C. 102(e) as being anticipated by Dropulic et al. (US Patent. No. 6,232,120B1) on the same ground as stared in the previous office action.

Applicants argue that Dropulic et al. provide no teaching, suggestion or indication of a method to inhibiting virus infection by interference with viral integration with a conditionally replicating viral vector. Accordingly, the cited reference failed to teach all of the limitations of the claimed invention, and the rejection should be withdrawn.

Applicants' argument has been respectfully considered; however, it is not found persuasive because this limitation was not present anywhere in the application as it was originally filed. This limitation is therefore, a new matter and should not be entered as well as read into the claims. Hence, the rejection is maintained.

Claims 1, 3-6, 8-9, 14-21 are still rejected under 35 U.S.C. 102(b) as being anticipated by Dropulic et al. (WO 97/20060A1) under the same ground as stated in the previous office action.

Applicants argue that Dropulic et al. provide no teaching, suggestion or indication of a method to inhibiting virus infection by interference with viral integration with a conditionally replicating viral vector. Accordingly, the rejection should be withdrawn.

Applicants' argument has been respectfully considered; however, it is not found persuasive because this limitation was not present anywhere in the application as it was original filed. This limitation is therefore, a new matter and should not be entered as well as read into the claims. Hence, the rejection is maintained.

Claims 1 and 3 are still rejected under 35 U.S.C. 102(b) as being anticipated by Welch et al. (Gene Ther. 1996, Vol. 3, pp. 994-1001) under the same ground as stated in the previous office action.

Applicants argue that the hepatitis C virus does not integrate into a host cell genome as part of its life cycle; the reference is thus directed to a different filed of endeavor and unrelated to the instant claims. Accordingly the rejection should be withdrawn.

Applicants' argument has been respectfully considered; however, it is not found persuasive because this limitation was not present anywhere in the application as it was originally filed. This limitation is therefore, a new matter, it should not be entered as well as read into the claims. Hence, the rejection is maintained.

Claims 1, 3 and 19 are still rejected under 35 U.S.C. 102(b) as being anticipated by Lieber et al. (J. Virol. 1996, Vol. 70, pp. 8782-8791) under the same ground as stated in the previous office action.

Applicants argue that Lieber et al. disclose observations with respective to hepatitis C virus, which does not integrate into a host cell genome as part of its life cycle; the reference is thus directed to a different filed of endeavor and unrelated to the instant claims. Accordingly the rejection should be withdrawn.

Applicants' argument has been respectfully considered; however, it is not found persuasive because this limitation was not present anywhere in the application as it was original filed. This limitation is therefore, a new matter, it should not be entered and read into the claims. Hence, the rejection is maintained.

Claims 1, 3-6, 8-9, and 14-21 are still rejected under 35 U.S.C. 102(b) as being anticipated by Venkatesh et al. (P.N.A.S. USA 1990, Vol. 87, pp. 8746-8750) on the same ground as stated in the previous office action.

Applicants argue that Venkatesh et al. disclose the use of a conditionally cytotoxic adenovirus vector to kill cells upon infection with HIV-1. There is no indication that the integration of HIV was inhibited by the adenovirus based vector. The cited reference failed to teach all of the limitation of the claims; therefore, the rejection should be withdrawn.

Applicants' argument has been fully considered, however, it is not found persuasive because the limitation was not present anywhere as the application was originally filed. This limitation is therefore, a new matter, it should not be entered and read into the claims.

Moreover, the claimed invention read on any or all-viral vector, the adenovirual vector is the condition replication vector, because it is only be replication in the condition when the complementary gene is existed in the host cells. Therefore, the rejection is maintained.

Claims 1-3, 6-7, 14-17 and 19 are still rejected under 35 U.S.C. 102(b) as being anticipated by Lu et al. (Cancer Gene Therapy, 1994, Vol. 1, pp. 267-277) on the same ground as stated in the previous office action.

Applicants argue that Lu et al. fail to disclose any effects relating to inhibition of HPV integration and thus fail to teach all of the limitations of the claims, the rejection should be withdrawn.

Applicants' argument has been respectfully considered; however, it is not found persuasive because this limitation was not present anywhere in the application as it was originally filed. This limitation is therefore, a new matter and should not be entered as well as read into the claims. Hence, the rejection is maintained.

Claims 1, 3-6and 8-21 are still rejected under 35 U.S.C. 102(b) as being anticipated by Alwine et al. (WO 94/16060A1) on the same ground as stated in the previous office action.

Applicants argue that Alwine et al. fail to disclose any effect relating to inhibition of HIV integration and thus fail to teach all limitations of the claimed invention. Accordingly, the rejection should be withdrawn.

Applicants' argument has been respectfully considered; however, it is not found persuasive because this limitation was not present anywhere in the application as it was originally filed. This limitation is therefore, a new matter and should not be read into the claims. Hence, the rejection is maintained.

Claims 1, 3-6 and 8-21 are still rejected under 35 U.S.C. 102(b) as being anticipated by Wong-Staal et al. (WO 94/26877A1) on the same ground as stated in the previous office action.

Applicants argue that Wong-Staal et al. fail to disclose any effect relating to inhibition of HIV integration and thus fail to teach all limitations of the claimed invention. Accordingly, the rejection should be withdrawn.

Applicants' argument has been respectfully considered; however, it is not found persuasive because this limitation was not appear anywhere in the application as it was originally filed. This limitation is therefore, a new matter and should not be entered as well as read into the claims. Hence, the rejection is maintained.

Claims 1, 3-6, 8-9, 14-17, 19-21 are still rejected under 35 U.S.C. 102(b) as being anticipated Zhou et al. (Gene 1994, Vol. 149, pp. 33-39) on the same ground as stated in the previous office action.

Applicants argue that Zhou et al. fail to disclose any effect relating to inhibition of HIV integration and teach all limitations of the claimed invention. Accordingly, the rejection should be withdrawn.

Applicants' argument has been respectfully considered; however, it is not found persuasive because this limitation was not appear anywhere in the application as it was originally filed. This limitation is therefore, a new matter and should not be entered as well as read into the claims. Hence, the rejection is maintained.

Claims are still rejected under 35 U.S.C. 102(b) as being anticipated Yu et al. (Virology 1995, Vol. 206, pp. 381-386) on the same ground as stated in the previous office action.

Applicants argue that Yu et al. fail to disclose any effect relating to inhibition of HIV integration and thus fail to teach all limitations of the claimed invention. Accordingly, the rejection should be withdrawn.

Applicants' argument has been respectfully considered; however, it is not found persuasive because this limitation was not appear anywhere in the application as it was originally filed. This limitation is therefore, is a new matter and should not be entered as well as read into the claims. Hence, the rejection is maintained.

Claims 1, 3-6, 8-9, 14-17 and 19-21 are still rejected under 35 U.S.C. 102(b) as being anticipated Ramezani et al. (Antisense Nucleic Acid Drug Dev. 1996, Vol. 6, pp. 229-235) on the same ground as stated in the previous office action.

Applicants argue that Romezani et al. fail to disclose any effect relating to inhibition of HIV integration and thus fail to teach all limitations of the claimed invention, Accordingly, the rejection should be withdrawn.

Applicants' argument has been respectfully considered; however, it is not found persuasive because this limitation was not present anywhere in the application as it was originally filed. This limitation is therefore, is a new matter and should not be entered as well as read into the claims. Hence, the rejection is maintained.

Claims 1, 3-6 and 89, 14-17, 19-21 are rejected under 35 U.S.C. 102(b) as being anticipated Lo et al. (Virology. 1992, Vol. 190, pp. 176-183) on the same ground as stated in the previous office action.

Applicants argue that Lo et al. fail to disclose any effect relating to inhibition of HIV integration and thus fail to teach all limitations of the claimed invention, Accordingly, the rejection should be withdrawn.

Applicants' argument has been respectfully considered; however, it is not found persuasive because this limitation was not present anywhere in the application as it was originally filed. This limitation is therefore, is a new matter and should not be entered as well as read into the claims. Hence, the rejection is maintained.

Claims 1, 3-6 and 8-21 are still rejected under 35 U.S.C. 102(b) as being anticipated Dropulic et al. (P.N.A.S. USA, 1996, Vol. 93, pp. 11103-11108) on the same ground as stated in the previous office action.

Applicants argue that Dropulic et al. fail to disclose any effect relating to inhibition of HIV integration and thus fail to teach all limitations of the claimed invention. Accordingly, the rejection should be withdrawn.

Applicants' argument has been respectfully considered; however, it is not found persuasive because the limitation was not present anywhere as the application was originally

filed. This limitation is therefore, a new matter and it should not be entered as well as read into the claim. Hence, the rejection is maintained.

Claims 1, 3-6, 8-9, 14-21 are still rejected under 35 U.S.C. 102(b) as being anticipated Dropulic et al. (J. Virol, 1992, Vol. 66, pp. 1432-1441).

Applicants argue that Dropulic et al. fail to disclose any effect relating to inhibition of HIV integration and thus fail to teach all limitations of the claimed invention. Accordingly, the rejection should be withdrawn.

Applicants' argument has been respectfully considered; however, it is not found persuasive because the limitation was not present anywhere in the application as it was original filed. This limitation is therefore, a new matter, and should not be entered and read into the claim. Hence, the rejection is maintained.

Claims 1, 3-6, 8-9, 14-21 are rejected under 35 U.S.C. 102(b) as being anticipated Macpherson et al. (Frontiers in Bioscience, June 1999, pp. 497-505) on the same ground as stated in the previous office action.

Applicants argue that Macpherson et al. fail to disclose any effect relating to inhibition of HIV integration and thus fail to teach all limitations of the claimed invention. Accordingly, the rejection should be withdrawn.

Applicants' argument has been respectfully considered; however, it is not found persuasive because the limitation was not present anywhere as the application was original filed. This limitation is therefore, a new matter and should not be entered as well as read into the claim. Hence, the rejection is maintained.

Claims 1, 3-6, 8-9, 14-17 and 19-21 arestill rejected under 35 U.S.C. 102(b) as being anticipated Sczakiel et al. (Methods in Molecular Biology 1997, Vol. 63, pp. 389-400) on the same ground as stated in the previous office action.

Applicants argue that Sczakiel et al. fail to disclose any effect relating to inhibition of HIV integration and thus fail to teach all limitations of the claimed invention. Accordingly, the rejection should be withdrawn.

Applicants' argument has been respectfully considered; however, it is not found persuasive because the limitation was not present anywhere in the application as it was original filed. This limitation is therefore, a new matter, and is should not be entered as well as read into the claim. Hence, the rejection is maintained.

New Ground of Rejection:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3-6 and 8-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dropulic et al. (WO 97/20060A1) and Macpherson et al. (Frontier in Bioscience , 1991, June 1, Vol. 4, pp. d497-505).

The claimed invention is directed to use a conditional replication HIV vector (crHIV) carrying an anti-HIV ribozyme for inhibiting the HIV infection, wherein the crHIV can be used with various dosages in term of MOI and the inhibition is interruption of the wild-type HIV integration into the host cells.

WO 77/20060A1 disclose a method of making a conditionally replicating viral vector, especially the HIV-1 based retroviral vector, which is characterized by a capacity to replicate only in a host cell that is permissive for replication of said vector in that the said vector comprises at least one nucleotide sequence, the presence, transcription or translation of which nucleotide confers to said vector in a host cell, a selective advantage over a wild-type strain of a virus corresponding to the virus from which said vector was derived or a helper. More preferably, the said conditional replicating HIV-1 vector is disclosed as construct derived from a wild type of the HIV-1 virus pNL4-3 strain and followed by insertion hammerhead anti-HIV ribozyme sequences in the ribozyme expression cassette. The said vector is further constructed

with a substitutive mutation at the ribozyme biding site, which enable the vector to escape from the ribozyme binding and degradation. The said vector is also disclosed with insertion of other selective gene sequence, such as a multidrug resistance gene to help the further selective over a host cell containing the wild-type virus. The disclosure of the WO 97/20060 also include a method for using the vector to inhibit the wild-type viral replication by contacting the CD4+ host cell with the said condition replication vector, to inhibit the wild-type HIV infection (See entire document, especially the example 1 on pages 56-61 and example 4 on pages 65-69 and claims 1-52). WO 77/20060A1 does not explain that the inhibition can influence at the step of HIV integration into the host cells.

However, the HIV life cycle is well known in the art as summarized by Machpherson et al. In general, the process of HIV infections includes several step, first, it is s fusion between the viral envelope protein with and target cell membranes through the receptor CD4 and co-receptor CXCR4 and CCR5 etc. Then, following viral particle entering the target cell, it is an uncoating process. Afterward, the viral genomic RNA (in complex with the viral proteins, integrase, polymerase and reverse transcriptase) enters the host cell cytoplasm and converted into cDNA or ds DNA by viral reverse transcriptase and polymerase enzymes. The cDNA, and a dsDNA copy of HIV virus is transported to the cell nucleus and then integrated into the host genome by the action of viral integrase protein (section of 2.1 on page 2 of 18). Machpherson et al. also teach that robozymes are catalytic RNA molecules with enzyme-like cleavage properties that can be designed to target specific RNA sequences within the HIV-1 genome (lines 5-7 on page 1 of 18). The therapeutic HIV ribozymes function to cleavage the HIV at different stages and render the virus to be defective for finishing its infectious life cycle, such as inability of integration, replication, transcription, translation (Fig. 2 on page 3 of 18).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention was filled to be motivated by the recited references and to combine the teaching taught by Droplic et al. and Macpherson et al to design a therapeutic HIV ribozyme particularly cleavage the wild-type HIV virus before the virus integration. As no unexpected results have been provided, hence the claimed invention as a whole is prima facie obvious absence unexpected results.

Regarding the modification of using different virus titers etc. this is generally recognized as being within the level of the ordinary skill in the art, In re Rose, 105 USPQ 237 (CCPA 1995) because it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the workable ranges involves only routine skill in the art, In re Aller, 105, USPQ 233. Hence, the claimed invention as a whole is prima facie obvious absence unexpected results.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bao Qun Li whose telephone number is 703-305-1695. The examiner can normally be reached on 8:00 to 4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 703-308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Bao Qun Li October 8, 2002

ALI R. SALIMI
PRIMARY EXAMINER